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# Overview

In this issue of *Neuron*, we feature fifteen reviews on topics related to neurological and psychiatric disease. The reviews were chosen to complement the topics and talks to be presented at this year's *Neuron* satellite meeting on "Neurons and Disease" at the Society for Neuroscience meeting (http://www.neuron-meeting.com) on October 12th and 13th. The speakers at the meeting will be Adriano Aguzzi, Mark Bear, Nancy Bonini, David Porteous, Louis Ptacek, Jeffrey Rothstein, Dennis Selkoe, Thomas Südhof, Nora Volkow, and Huda Zoghbi. We are still accepting registrations for the meeting.

In considering potential topics for this series, there was certainly no shortage of subject matter to choose from. Tragically, there are far too many ways that the complex machine that is our brain can go awry. Clearly, we could not cover adequately every major disease or even category of diseases in this series. The challenge was to narrow down the possibilities to a focused group of reviews. Our aim was to highlight the rich biology and diversity of mechanisms that characterize diseases of the nervous system, and we have selected topics that we think illuminate common principles, mechanisms, or approaches that go beyond a particular disease. The reviews as a whole spotlight the challenges associated with unraveling disease mechanisms in an organ as complicated as the brain and point to the importance of integrating multiple types of approaches and multiple levels of analyses to understanding disease.

November 3rd marks the 100th anniversary of the lecture from Alois Alzheimer presenting the first case of a patient with a neural pathological disease characterized by progressive dementia that came to be known as Alzheimer's disease. It seems fitting to pay tribute to this event in this series. In his essay, "A Hundred Years of Alzheimer's Disease Research," John Hardy reviews the progress in the field in the intervening century and suggests where the remaining challenges lie. Hardy suggests that there have been three periods of Alzheimer's research—the first led to the definition of the clinical phenotype, the second involved a neurochemical assessment of the disease, and the third, the current period, is the application of molecular biological and genetic approaches to investigate underlying mechanisms with an ultimate goal of translating these mechanistic insights into therapies. The review from Scott Small and Sam Gandy also covers Alzheimer's disease. Small and Gandy argue that a cell biological understanding of Alzheimer's disease may be key to deciphering this disease. Their review discusses recent results suggesting a contribution of protein sorting pathways and deficits to Alzheimer's pathogenesis. Just as has been the case for Alzheimer's disease, for many of the more classical neurodegenerative diseases, such as Parkinson's disease, Huntington's disease, ALS, and multiple sclerosis, genetics has been key to providing insights into potential pathways and mechanisms, but cell biology has been critical for building mechanistic models for how these genes and pathways function in a biological context. In their review, Virginia Lee and John Trojanowski discuss the mechansisms of $\alpha$-synuclein-mediated neurodegeneration and propose drug discovery approaches for identifying therapies that target $\alpha$-synuclein. The formation of inclusion bodies and protein aggregates that is the hallmark of $\alpha$-synuclein pathologies is turning out to be a common phenotype for a broad range of disorders. Whether these inclusions play a causal role in pathogenesis or are simply a marker of the disease or are even a protective cellular mechanism remains unclear.

Many classes of neurodegenerative diseases appear to impact specific populations of neurons or regions of the brain preferentially, and a key question is what accounts for the selective vulnerability of certain classes of neurons to certain pathologies. For example, ALS is a disease that selectively impacts motor neurons. Séverine Boillée, Christine Vande Velde, and Don Cleveland review our current understanding of ALS pathogenesis and address this question in their review, arguing that this selective vulnerability stems from a combination of multiple mechanisms, involving not just the motor neurons but also neighboring glia and other nonneuronal cells, including cells of the immune system. Indeed, as several of the reviews in the series highlight, while the contribution of the immune system has been largely ignored for many diseases of the CNS (or was thought to be a marker and consequence of the disease, not a causal element) there is increasing support for a role of inflammation and immune mechanisms in many diseases of the nervous system. For instance, it is clear that inflammation and the immune response is a key factor in multiple sclerosis, and in their review, Stephen Hauser and Jorge Oksenberg review recent developments in understanding the etiology and disease pathogenesis of multiple sclerosis, including the contribution of the immune system. Recent work on multiple sclerosis also highlights this theme of interactions between multiple cell types contributing to pathology. Multiple sclerosis has long been thought to be a myelin disease. However, there is now a large body of work to show that damage to axons and neuronal loss precede the loss of myelin and may play a key role in some of the neurological dysfunctions associated with the disease. There is also strong evidence to suggest a key role for the immune system in neuropathic pain. James Campbell and Richard Meyer review current understanding of the the mechanisms of neuropathic pain, with a particular focus on peripheral nerve pathologies. Continuing on the theme of immune contributions to diseases of the nervous system, the review from Angela Vincent, Bethan Lang, and Kleopas Kleopa on autoimmune channelopathies discusses the role of autoantibodies in various neurological diseases.

As many of the reviews in this series spotlight, molecular genetics has proven to be a powerful tool for cracking open many of these diseases. For diseases like Alzheimer's and Parkinson's, some of the greatest insights into disease pathogenesis have come from the identification of genes associated with rare familial forms of these diseases, which in turn shed light on

other interactions and pathways. It is important to remember that genetic contributions can be more complicated than point mutations, deletions, simple truncations, or simple Mendelian genetics. The review by Jennifer Lee and James Lupski explores more complex genomic mechanisms and their contribution to diseases of the nervous system. Lee and Lupski discuss diseases that are caused not by the classic type of genetic lesion resulting in singular changes in the DNA sequence of a particular coding region but rather are due to genomic rearrangements that lead to a change in gene copy number and dosage. The review from Donny Licatalosi and Robert Darnell on the role of splicing regulation in neurologic disease highlights another form of genomic complexity—alternative splicing. There are more and more examples of alternatively spliced mRNAs in the nervous system, including alternatively spliced ion channels, membrane receptors, and other regulatory proteins. In most cases, the precise impact of the different splice isoforms and their regulation on neuronal function is only beginning to be understood.

Arguably, we have advanced more quickly in our understanding of the causes of neurodegenerative diseases, like Alzheimer's, Parkinson's, multiple sclerosis, ALS, Huntington's, and other polyglutamine disorders, than we have in deciphering psychiatric diseases, like schizophrenia and depression, or complex neurodevelopmental disorders, like autism. Both the complexity of the clinical phenotypes of these diseases (which, in most cases, are actually a spectrum of disorders rather than a single disease) and the fact that these diseases are multifactorial, involving many genes and multiple systems, may contribute to the slower pace of discovery. Christopher Ross, Russell Margolis, Sarah Reading, Mikhail Pletnikov, and Joseph Coyle review recent progress in our understanding of schizophrenia, both with respect to the clinical features of the disease and the underlying neuropathologies. Schizophrenia, like many psychiatric disorders, is a disease involving multiple neural systems. There has been some data to suggest that neuronal synchrony, the coordinated interactions of networks of neurons across multiple brain regions, may contribute to the cognitive impairments associated with schizophrenia. The review from Peter Uhlhaas and Wolf Singer discusses potential links between defects in neural synchronization and the behavioral and cognitive dysfunctions associated with disorders like schizophrenia, epilepsy, autism, and Alzheimer's and Parkinson's diseases.

Animal models have been a critical tool for understanding diseases of the nervous system, and two of the reviews in this series discuss the contributions that different types of animal models can have for both deciphering disease mechanisms and for assessing therapeutics. Such models are not without major caveats; quite obviously, neither the mouse brain nor the *Drosophila* brain is a perfect model of the human brain. In their review, P. Alexander Arguello and Joseph Gogos discuss the challenges associated with developing models for psychiatric diseases like schizophrenia, which encompass a complex disease phenotype and etiology. J. Lawrence Marsh and Leslie Thompson discuss the contributions that lower invertebrate model systems, like *Drosophila*, have made toward understanding neurodegenerative disease and the advantages that *Drosophila*, with its ease of manipulation and powerful genetics, offers both for dissecting disease mechanisms and for screening potential therapies.

The ultimate aim of all of the research into disease mechanisms is to find a cure and to alleviate the tremendous human suffering associated with each of these diseases. Two reviews in this issue discuss two very promising forms of therapy that even a few years ago might have been thought to be futuristic and more science fiction than practical reality. Thomas Wichmann and Mahlon DeLong discuss the potentials of deep brain stimulation as a therapeutic approach for movement disorders and some classes of psychiatric diseases. Andrew Schwartz, Tracy Cui, Douglas Weber, and Daniel Moran discuss the potential applications for neural prosthetics for the treatment of motor disorders.

The goal of this review series is to highlight the significant advances in understanding diseases of the nervous system that have been made in recent years. We hope that we have been able to capture the excitement in the field and that you will find these reviews interesting and informative. There is still much we don't know and much work to be done, but there are reasons to be optimistic.

We are grateful for the efforts of all of the authors in this series and also the anonymous reviewers who provided feedback on the reviews. To close, we would like to say a few words about the cover art, which is an adaptation of an oil painting by Bryan Charnley, an artist who suffered from paranoid schizophrenia. The painting is entitled *Self Portrait, 6th May 1991* and is from a series of pieces that he painted during a period of time while experimenting with varying dosages of the drugs used to control his disease. We would like to thank the UK-based mental health charity SANE and the family of the artist for granting permission to use this image for the cover art. The painting beautifully depicts the tragedy and disarray associated with this disease, and the question mark at the center of the bulls-eye target on the artist/subject's head speaks loudly for the many questions and challenges that still remain in this field.